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Introduction

"*Genes and Genetics in Hypertension and Vascular Disease*" was the theme of the International Society of Nephrology's recent Forefronts in Nephrology meeting in Groβ Dölln, outside of Berlin. The aim of the Forefronts series is to present the state-of-the-art in different aspects of nephrology, which includes the unresolved and current problems in the field. In that way, active investigators, particularly our younger colleagues, can be exposed to the current, often vexing problems of a particular arena of study. This symposium on "*Genes and Genetics of Hypertension*" was broad in scope and encompassed four major areas highly relevant to vascular disease: (*1*) complex genetic diseases; (*2*) animal models; (*3*) gene targeting; and (*4*) the genetics of hypertension, diabetes, and obesity in humans. Furthermore, young investigators were given the opportunity to present posters on their most recent work and received criticism and praise as the material dictated. All this occurred in an environment of dense forest, a sparkling lake, ample physical exercise, and pleasant evenings with wine and song.

Complex genetics encompasses complicated mathematics. From the contribution of Francoise Clerget-Darpoux, the current diverse strategies were presented. The merits and demerits of linkage and association studies were argued by Hywel Jones and Thomas Wienker. Evaluation of candidate genes and the identification of disease susceptibility loci by means of association studies was critically appraised by linkage experts who instead favor the noncommittal approach of a total genome scan to find loci linked to a phenotype. The latter requires approximately 700 affected sibling pairs in the case of hypertension. Furthermore, since hypertension arises in adulthood, and often later adulthood, the likelihood of obtaining samples from the parents of affected persons is limited. Newer strategies, such as haplotype relative risk approaches through the analysis of trios, siblings and one parent, may offer alternatives to case-control association studies.

"Bioinformatics" is a formidable, almost teutonic, term. What does it mean and what are we to do with it? A round table was used to introduce the audience to the topic. Jens Reich and André Reis lead the audience through the jungle of the genetics information highway. Access to databases, living with "Blast," ESTs, where to go when you are cloning positionally, and how to survive exon trapping, were some of the topics discussed.

The practical aspects of recruitment were presented by Herbert Schuster, who has developed a program in which index patients recruit their family members. Mailers with questionnaires and EDTA blood tubes are sent, the family physicians are included in the process, and confidentiality is assured. With this method, Herbert has recruited about 1000 families with lipid disturbances. The cover of this issue of *Kidney International* features an output from Herbert's oligonucleotide ligation assay (OLA) for the diagnosis of familial hypercholesterolemia. This test permits the simultaneous detection of many (200 if necessary) gene mutations. A multicolor gel file shows primary data from one OLA experiment with DNA from 16 individuals. Every band represents a ligation product of a particular allele. Ligation products from mutant alleles are easily detected as extra bands. A genotyper software program analyzes the pattern of bands and produces a standard data file reporting "positive" results of the test to the investigator.

Andreas Busjahn presented twin studies that permit heritability estimates by comparing intrapair variability between monozygotic and dizygotic twins, and then a modified sibling pair analysis in dizygotic twins to identify quantitative trait loci. With this technique, he has shown linkage between the IGF-1 gene locus, blood pressure, and heart size.

"What to do with the samples" is an area moving at a ferocious pace. Margret Hoehe presented multiplex sequencing, with which she can sequence genes or gene segments highly efficiently in large numbers of subjects. As an example, she presented data from the Bergen Hypertension Study, in which she sequenced the entire β-adrenoceptor gene in 60 people. The results were revealing. Steve Lombardi presented the latest "high tech" approaches being developed by industry to keep up the pace. Gooey gels are likely to be replaced by chips and mass spectroscopy techniques.

The next session concentrated on animal models. Detlev Ganten had already given an overview on transgenic rat models. Andreas Schedl presented the possibilities offered by heterologous knock out models and cre-lox knock out models. He provided tantalizing glimpses into the development of the kidney and the role of Wilm's tumor suppressor gene, WT1. Is hypertensive nephrosclerosis influenced by genetic variance? Clinical observations suggest that black Americans have a greater propensity to develop hypertension-induced renal injury compared to whites. Dahl salt-sensitive rats develop more renal injury than spontaneously hypertensive rats (SHR). Ted Kurtz provided compelling evidence to support this hypothesis. In SHR made congenic for the brown Norway (BN) histocompatility locus, he and his associates transplanted kidneys, such as BN kidneys resided in an SHR, which retained its native kidney. The kidneys were exposed to precisely the same environment. Guess which kidney did better or worse? Alan Deng provided insight into the Dahl salt-sensitive hypertensive rat. Quantitative trait loci were unraveled and the roles of nitric oxide in this important hypertensive model were elucidated. Yoram Yagil and Chana Yagil have worked for years on the Sabra rat, a salt sensitive model established by Drori Ben Ishay. This model is unique in that the salt resistant strain is resistant to DOCA-salt hypertension, compared to the salt sensitive strain. New gene loci responsible for this phenomenon have been identified. Again, nitric oxide cropped up. Another inbred strain was discussed by Pavel Hamet. Here we need more data. The session was closed by John Hunter, who presented studies on gene-manipulated mice (input).

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After a 10 kilometer run in and around the lake, the next day began with a session on somatic gene transfer in cardiovascular disease. Oliver Smithies elegantly showed that genes can be "duplicated" or "triplicated," etc., in the same animal to show a gene dosage effect. The influence of renin-angiotensin system genes on blood pressure and other attributes was exposed in a "knock your socks off" fashion. The power of molecular biology was never as obvious as in this presentation.

Peter Carmeliet, a wine expert from Belgium, concentrated on the coagulation system and demonstrated how knock outs of tissue factor illustrates the surprising importance of this and other factors on vascular structure and their role in the repair of injured vessels. Julie Chao and her husband Lee used somatic gene transfer of the kallikrein gene to investigate the role of this protein in blood pressure regulation.

Hermann Haller gave insight into antisense approaches in the therapy of vascular disease. He demonstrated that certain protein kinase C isoforms, notably PKC a, are important in mediating glucose-induced and hypoxia-induced endothelial damage. Antisense oligodinucleotides (ODN) can ameliorate these effects. Most impressive were the data in a model of reperfusion injury. Here, antisense directed against the intercellular adhesion molecule (ICAM)-1 protected against reperfusion injury. Preliminary animal data suggest that antisense therapy may be important in transplantation medicine.

Next, the group moved to specific genetic challenges in humans. Florent Soubrier has been the most active human geneticist exploring the renin-angiotensin system. The insertion/deletion angiotensin converting enzyme gene polymorphism, the angiotensinogen M235T substitution, and a polymorphims in the AT1 receptor gene have captivated his interest. Most puzzling is the angiotensin converting enzyme insertion/deletion (ACE I/D) polymorphism, which does not seem to influence blood pressure *per se*, but nevertheless has a surprising influence on cardiovascular risk, heart size, stroke, diabetes, and the course of nephrosclerosis.

Giuseppe Bianchi presented the most elegant sequence of events. His group has been the first to find a hypertension-relevant gene in the rat and elucidated the function of that gene. Adducin is a cytoskeletal protein that influences the function of the sodium pump, and mutations in this gene affect sodium reabsorption. The Milan rat led the way to elucidating salt sensitivity. Bianchi's group has now found a mutation in the human adducin gene. By association and linkage techniques, they have implicated this mutation in salt sensitive hypertension and to the response from thiazide diuretics.

Wilhelm Weitz was the first to implicate genetics in hypertension over 80 years ago. Weitz performed case control, sibling pair, and twin studies, and concluded that hypertension is a monogenic disease. George Pickering proved that Weitz was wrong. But was he? David Simon led us through a series of salt- and water-related monogenic syndromes. Some, like glucocorticoid-remediable aldosteronism, Liddle's syndrome, and the syndrome of apparent mineralocorticoid excess, cause hypertension. Interestingly, alternative syndromes exist. For instance, Gitleman's syndrome is caused by a mutated Na/Cl distal tubular transporter, and Bartter's syndrome is caused by a defective Na2ClK transporter. These conditions have given us amazing insight into salt and water metabolism.

Sylvia Bähring celebrated her birthday by telling us about a monogenic syndrome not related to salt and water balance. Autosomal-dominant hypertension and brachydactyly is an unusual condition described in Turkey, Canada, and the United States. The hypertension is severe, causes stroke, and cosegregates 100% with brachydactyly. Affected persons exhibit accelerated fibroblast growth in culture, which has also been described in essential hypertension and animal models. Sylvia showed differential display data and other functional cloning approaches. Cloning this gene may give important insights into essential hypertension.

The final discussion dealt with metabolic disorders. Graeme Bell carried us back to southern Texas, Starr county to be exact. In an affected sibling study, his group found an exciting gene locus for type II diabetes mellitus on chromosome 3. (By the way, Greame Bell and Matthias Köhler were also the fastest participants in the 10K race, although Heini Murer received the age-related runner's prize. Friedrich Luft, unfortunately, fell off the pace.) Kumar Sharma discussed obesity and the OB gene in the pathogenesis of that condition. Interestingly, the OB gene has specific relevance to decreased renal function and to patients requiring dialysis treatments.

Whither from here? We believe that this Forefronts in Nephrology topic could be held every two years and contain entirely new information. Insights into genes and genetic studies are rapidly unfolding from many directions because of new technology, cross fertilization of ideas, and more specialized tools for scientific discovery. Indeed, the future is now.

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